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Mismatch Repair Deficiency, Microsatellite Instability, and Survival

An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial

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IMPORTANCE Mismatch repair (MMR) deficiency (MMRD) and microsatellite instability (MSI) are prognostic for survival in many cancers and for resistance to fluoropyrimidines in early colon cancer. However, the effect of MMRD and MSI in curatively resected gastric cancer treated with perioperative chemotherapy is unknown.

OBJECTIVE To examine the association among MMRD, MSI, and survival in patients with resectable gastroesophageal cancer randomized to surgery alone or perioperative epirubicin, cisplatin, and fluorouracil chemotherapy in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial.

DESIGN, SETTING, AND PARTICIPANTS This secondary post hoc analysis of the MAGIC trial included participants who were treated with surgery alone or perioperative chemotherapy plus surgery for operable gastroesophageal cancer from July 1, 1994, through April 30, 2002. Tumor sections were assessed for expression of the MMR proteins mutL homologue 1, mutS homologue 2, mutS homologue 6, and PMS1 homologue 2. The association among MSI, MMRD, and survival was assessed.

MAIN OUTCOMES AND MEASURES Interaction between MMRD and MSI status and overall survival (OS).

RESULTS Of the 503 study participants, MSI results were available for 303 patients (283 with microsatellite stability or low MSI [median age, 62 years; 219 males (77.4%)] and 20 with high MSI [median age, 66 years; 14 males (70.0%)]). A total of 254 patients had MSI and MMR results available. Patients treated with surgery alone who had high MSI or MMRD had a median OS that was not reached (95% CI, 11.5 months to not reached) compared with a median OS among those who had neither high MSI nor MMRD of 20.5 months (95% CI, 16.7-27.8 months; hazard ratio, 0.42; 95% CI, 0.15-1.15; $P = .09$). In contrast, patients treated with chemotherapy plus surgery who had either high MSI or MMRD had a median OS of 9.6 months (95% CI, 0.1-22.5 months) compared with a median OS among those who were neither high MSI nor MMRD of 19.5 months (95% CI, 15.4-35.2 months; hazard ratio, 2.18; 95% CI, 1.08-4.42; $P = .03$).

CONCLUSIONS AND RELEVANCE In the MAGIC trial, MMRD and high MSI were associated with a positive prognostic effect in patients treated with surgery alone and a differentially negative prognostic effect in patients treated with chemotherapy. If independently validated, MSI or MMRD determined by preoperative biopsies could be used to select patients for perioperative chemotherapy.

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Supplemental content

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Gastric cancer is the fifth most common cancer and the third most common cause of cancer-related death globally.[1] In Western countries, patients with operable gastric or gastroesophageal adenocarcinoma frequently undergo neoadjuvant or perioperative chemotherapy before surgical resection.[2,3] This adjunctive chemotherapy is associated with a modest benefit in terms of overall survival (OS) compared with surgery alone but also with toxic effects, including neutropenia and thromboembolic disease. Unfortunately, after optimal multimodality therapy, approximately half of patients undergoing resection will relapse and die of their cancer. There are no validated prognostic biomarkers for patients with gastroesophageal cancer who receive neoadjuvant treatment, and current patient selection is based purely on preoperative radiologic staging.

Microsatellite instability (MSI) and mismatch repair (MMR) deficiency (MMRD) are positively prognostic for survival in patients with stage II colon cancer and may be negatively prognostic for the efficacy of fluoropyrimidine adjuvant chemotherapy in the same patient group.[4,5] As a consequence, MMR protein status assessment is recommended by the National Comprehensive Cancer Network and the European Society for Medical Oncology guidelines for patients with resected stage II colorectal cancer before adjuvant chemotherapy.[6,7] For patients with gastric cancer, the prognostic effect of MSI has been suggested in several studies.[8-11] However, these studies are all retrospective, and each lacked a control group.

The United Kingdom Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial was an open-label, multicenter, phase 3 randomized clinical trial that compared the effect of 6 cycles of perioperative epirubicin, cisplatin, and infused fluorouracil chemotherapy (3 cycles before and 3 cycles after resection) plus surgery with surgery alone in patients with resectable gastroesophageal cancer.[2] Patients treated with perioperative chemotherapy had improved OS compared with patients treated with surgery alone (5-year OS, 36% vs 23%; hazard ratio [HR], 0.75; 95% CI, 0.60-0.93; P = .009). As a result, perioperative epirubicin, cisplatin, and fluorouracil chemotherapy became one standard treatment regimen for patients with resectable gastroesophageal adenocarcinoma. The objectives of this work were to establish the proportion of patients with high MSI (MSI-H) or MMRD cancer in the MAGIC cohort and to evaluate whether the presence or absence of these biomarkers had a prognostic effect on survival in patients treated with surgery alone or chemotherapy plus surgery.

Key Points

Question Do patients with operable gastroesophageal cancers with high microsatellite instability have different survival compared with patients with microsatellite-stable gastroesophageal cancer when treated with surgery alone or surgery plus perioperative chemotherapy?

Findings Patients with operable gastroesophageal cancer with high microsatellite instability have superior survival compared with patients with gastroesophageal cancer with low miscrosatellite instability or microsatellite stable tumors when treated with surgery alone. However, patients with operable gastroesophageal cancer with low miscrosatellite instability or microsatellite stable tumors have superior survival compared with patients with gastroesophageal cancer with high microsatellite instability when treated with perioperative chemotherapy plus surgery.

Meaning Patients with operable gastroesophageal cancer with high microsatellite instability did not benefit from perioperative chemotherapy. Alternative treatment approaches should be investigated for these patients.

Methods

MSI Assessment

This secondary analysis of the MAGIC trial included participants who were treated with surgery alone or perioperative chemotherapy plus surgery for operable gastroesophageal cancer from July 1, 1994, through April 30, 2002. Genomic DNA was extracted from macrodissected cancer and noncancer tissue using the QIAamp DNA FFPE Tissue Kit (Qiagen). The MSI status was determined using the Promega MSI Analysis System (Promega Corp). A detailed description of the MSI assessment method is in the eMaterial in the Supplement.

Tumors were classified as microsatellite stable (MSS) when all markers were stable, as having low MSI (MSI-L) when only 1 marker was unstable, and as MSI-H with minimum instability in 2 markers.[12] The term *instability* in this context refers to the presence of an increased number of nucleotide repeats in tumor than in the nontumor control DNA for each sample. The MSI-L and MSS tumors were combined for analysis as per previous analyses in gastric cancer.[10,13]

MMR Protein Assessment

For MMR protein immunohistochemical analysis, 3- to 4-µm sections were prepared from the tissue microarray blocks and stained for the mutL homologue 1 (MLH1), mutS homologue 2 (MSH2), mutS homologue 6 (MSH6), and PMS1 homologue 2 (PMS2) proteins. The eMaterial in the Supplement provides a detailed description of the immunohistochemical analysis method.

Loss of MMR protein expression (MMRD) was designated when none of the neoplastic epithelial cells had nuclear staining while positive internal control nuclei (lymphocytes and stromal cells) were present in the immediate vicinity of the tumor infiltrate. Normal expression was defined as the presence of nuclear staining of tumor cells irrespective of the proportion or intensity.

Tumor Regression Grading Assessment

Two pathologists (M.F., M.R.), who were masked to the treatment arm, reviewed the slides from all cases and graded the pathologic response using the Mandard tumor regression grading (TRG) system.[14] Differences in opinion were resolved by discussion.

Statistical Analysis

Overall survival was calculated from surgery to death from any cause or the last date of follow-up.[2] Progression-free survival

was calculated from surgery to the first event (ie, local recurrence or progression, distant recurrence, or death from any cause). Date of surgery was selected as the baseline for biomarker analysis to reduce potential bias because only patients with a surgical specimen were available for inclusion. Analyses were mainly performed within treatment arms because of the differences in timing of surgery to reduce potential bias in the estimates of effects. Interactions between treatment arm and biomarker status were used to highlight potential differences in prognostic effect and were assessed using a Cox proportional hazards regression model. Date of surgery could not be confirmed for 9 patients in the chemotherapy plus surgery arm, and these patients were excluded from the survival analyses. Differences in OS by MSI and MMR protein status were assessed using the Kaplan-Meier method and compared using Cox proportional hazards regression. The Cox proportional hazards regression model was univariate for MSI and MMRD status. All MMR proteins were assessed individually and as a group to include any absent MMR protein. $P < .05$ was considered statistically significant using 2-sided Cox proportional hazards regression. All analyses were conducted using STATA software, version 14 (StataCorp).

Results

MSI Prevalence and Clinical Characteristics

The MSI results were available for 303 patients (of 456 patients who had undergone resection). Because the data were obtained from resection specimens and analyses examine survival from the date of surgery, only patients who had undergone surgery (456 of 503 enrolled in the MAGIC trial) are potentially included (eFigure in the Supplement).

No difference was found in median survival between patients who had tissue available for MSI analysis and those who did not (20.7 [95% CI, 17.5-28.3] vs 17.9 [95% CI, 13.5-24.2]; HR, 0.91; $P < .48$). Twenty patients (6.6%) had MSI-H, and 2 (0.7%) had MSI-L. The rate of D2 resection in patients with MSI-H was 55% (vs 41% in the entire MAGIC trial population), and proportions of D2 resections for patients with MSI-H were similar in both arms. Resections were considered by the surgeon to be curative in comparable numbers of patients with MSI-H treated with surgery and surgery plus chemotherapy.

All MSI-H tumors were located in the stomach vs the gastroesophageal junction and esophagus (20 stomach cancers vs 0 gastroesophageal or esophageal tumors, $P = .04$). A total of 20 of the 234 stomach cancers (8.5%) had MSI-H (**Table 1**). The site of the tumor was not prognostic for survival. Patients with MSI-H tumors compared with MSS or MSI-L tumors were more frequently female and had an older median age. The MSI-H tumors were more frequently of Lauren intestinal histologic subtype and less commonly had metastatic lymph nodes in the resection specimen. None of these differences were statistically significant. A total of 4 (44.4%) of the 9 patients with MSI-H were treated with postoperative chemotherapy, consistent with the proportion of patients in the total trial population.

Table 1. Clinicopathologic Characteristics of Patients With MSS or MSI-L vs MSI-H[a]

Characteristic	MSS or MSI-L (n = 283)	MSI-H (n = 20)	*P* Value
Age, median (IQR) [range], y	62 (54-69) [23-79]	66 (60-69) [36-76]	.18
Sex			
Male	219 (77.4)	14 (70.0)	.42
Female	64 (22.6)	6 (30.0)	
Site of tumor			
Stomach	214 (75.6)	20 (100)	.04
Esophagus	37 (13.1)	0	
Gastroesophageal junction	32 (11.3)	0	
Histologic subtype			
Diffuse	75 (26.5)	2 (10.0)	.25[b]
Intestinal	163 (57.6)	15 (75.0)	
Mixed or other	35 (12.4)	2 (10.0)	
Missing	10 (3.5)	1 (5.0)	
T stage			
T1	12 (4.2)	0	.18[b]
T2	88 (31.1)	11 (55.0)	
T3	169 (59.7)	8 (40.0)	
T4	5 (1.8)	0	
Missing	8 (2.8)	1 (5.0)	
N stage			
N negative	54 (19.1)	6 (30.0)	.21[b]
N positive	156 (55.1)	8 (40.0)	
Missing	73 (25.8)	6 (30.0)	

Abbreviations: IQR, interquartile range; MSI-H, high microsatellite stability; MSI-L, low microsatellite stability; MSS, microsatellite stable.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Excluding those with missing data.

MSI and Pathologic Response to Chemotherapy

No patient with an MSI-H tumor treated with chemotherapy had a significant pathologic response as measured by a Mandard TRG of 1 or 2 (vs 3-5) in the resection specimen. Of patients with MSS or MSI-L tumors treated with chemotherapy, 20 of 123 (16.3%) had a TRG 1 or 2 response ($P = .22$ for MSI-H vs MSS or MSI-L). The κ between the 2 pathologists for TRG assessment was 0.64, which increased to 0.70 when the TRG was grouped as TRG 1 and 2 (responders) vs TRG 3 to 5 (nonresponders).

MMRD Prevalence and Clinical Characteristics

Assessment of the MMR protein was performed in 288 MLH1 cases, 282 MSH2 cases, 281 MSH6 cases, and 273 PMS2 cases. The different numbers of cases assessable for each protein reflect exhaustion of tumor material in selected tissue microarrays and resection blocks. All 4 MMR proteins were assessable in 268 cases. In 15 of 288 cases (5.2%), MLH1 was absent; PMS2 was absent in 17 of 273 cases (6.2%); MSH2 was absent in 3 of 282 cases (1.1%); and MSH6 was absent in 2 (0.7%) of 281 cases. Association with MMRD with clinicopathologic characteristics was similar to that for MSI (**Table 2**).

Table 2. Clinicopathologic Characteristics of Patients With MMRD vs MMRP[a]

Characteristic	MMRP (n = 246)	MMRD (n = 22)	*P* Value
Age, median (IQR) [range], y	61 (54-69) [23-79]	66 (61-68) [36-76]	.19
Sex			
Male	190 (77.2)	18 (81.8)	.79
Female	56 (22.8)	4 (18.2)	
Site of tumor			
Stomach	183 (74.4)	22 (100)	.02
Esophagus	34 (13.8)	0	
Gastroesophageal junction	29 (11.8)	0	
Histologic subtype			
Diffuse	67 (27.2)	2 (9.1)	.07[b]
Intestinal	138 (56.1)	17 (77.3)	
Mixed or other	32 (13.0)	1 (4.5)	
Missing	9 (3.7)	2 (9.1)	
T stage			
T1	10 (4.1)	0	.18[b]
T2	72 (29.3)	11 (50.0)	
T3	151 (61.4)	9 (40.9)	
T4	5 (2.0)	0	
N stage			
N negative	51 (20.7)	3 (13.6)	1.00[b]
N positive	135 (54.9)	9 (40.9)	
Missing	60 (24.4)	10 (45.5)	

Abbreviations: IQR, interquartile range; MMRD, mismatch repair deficiency; MMRP, mismatch repair proficiency.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Excluding those with missing data.

MMRD and Pathologic Response to Chemotherapy

No patient with MMRD cancer treated with chemotherapy had a good pathologic response to chemotherapy (defined as TRG 1 or TRG 2) compared with 14 of 100 patients (14.0%) with MMR proficiency (MMRP) ($P = .36$ for comparison of MMRP and MMRD).

Correlation of MMRD With MSI Status

A total of 254 patients had MSI and MMR results available. Of these, 15 of 17 MSI-H tumors had MMRD detected. Thirteen of 15 MLH1-negative tumors (86.7%) with available MSI results had MSI-H tumors compared with 4 of 239 MLH1-positive tumors (1.7%). This finding results in a sensitivity of MLH1 deficiency testing for MSI prognosis of 76.5% (95% CI, 50.1%-93.2%) and a specificity of 99.2% (95% CI, 97.0%-99.9%). All patients with absent MSH2 and MSH6 had MSI-H tumors. Twelve of 16 patients (75.0%) with absent PMS2 and MSI results had MSI-H tumors compared with 4 of 236 patients (1.7%) with PMS2-positive tumors. Overall concordance between MSI-H and MMRD status was 97.6% (eTable in the Supplement).

Survival Analysis

MSI and Survival

For patients treated with surgery alone, OS was better for patients with MSI-H than for patients with MSS or MSI-L because median OS was not reached for patients with MSI-H (95% CI, 4.4 months to not reached), whereas the median OS for patients with MSS and MSI-L was 20.3 months (95% CI, 16.7-27.7 months; HR, 0.35; 95% CI, 0.11-1.11; $P = .08$) (**Figure 1**). For patients treated with chemotherapy plus surgery, OS was better for patients with MSS or MSI-L (median OS, 22.5 months; 95% CI, 16.1-42.1 months), whereas median OS for patients with MSI-H was 9.6 months (95% CI, 0.1-21.9 months; HR, 2.22; 95% CI, 1.02-4.85; $P = .04$) ($P = .007$ for the interaction between MSI and treatment for OS) (Figure 1).

MMRD and Survival

Patients treated with surgery alone who had MMRD had a median OS that was not reached (95% CI, 4.4 months to not reached); for patients with MMRP tumors, the median OS was 20.7 months (95% CI, 17.5-28.6 months; HR, 0.40; 95% CI, 0.13-1.26; $P = .12$) (**Figure 2**). Patients treated with chemotherapy plus surgery who had MMRD had a median OS of 9.7 months (95% CI, 0.2-42.4 months); for patients with MMRP treated with chemotherapy, the median OS was 20.1 months (95% CI, 15.5-35.7 months; HR, 1.62; 95% CI, 0.81-3.26; $P = .18$) ($P = .04$ for the interaction between MMR protein status and survival).

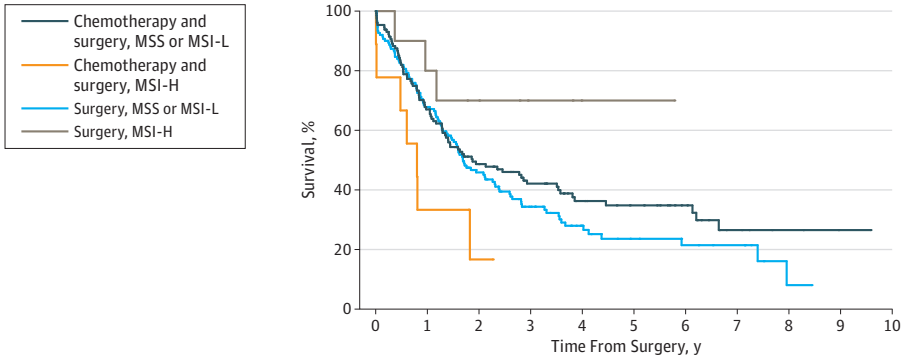
MSI and/or MMRD and Survival

Patients treated with surgery alone who had either MSI-H or MMRD had better OS than did patients who had neither MSI-H nor MMRD; median survival was not reached (95% CI, 11.5 months to not reached) for the MSI-H or MMRD group compared with those who had MSS or MSI-L, who had a median OS of 20.5 months (95% CI, 16.7-27.8 months; HR, 0.42; 95% CI, 0.15-1.15; $P = .09$). After treatment with chemotherapy plus surgery, patients who had either MSI-H or MMRD had a median OS of 9.6 months (95% CI, 0.1-22.5 months) compared with those who had neither MSI-H nor MMRD, who had a median OS of 19.5 months (95% CI, 15.4-35.2 months; HR, 2.18; 95% CI, 1.08-4.42; $P = .03$).

Discussion

Our study is the first, to our knowledge, to report the differentially prognostic effects of MSI and MMR protein expression on survival in a randomized clinical trial with a nonchemotherapy control arm for perioperatively treated gastroesophageal cancer. We found that patients with MSI-H or MMRD tumors have superior survival compared with patients with MSS/MSI-L or MMRP tumors when treated with surgery alone and conversely have inferior survival to patients with MSS/MSI-L or MMRP tumors when treated with perioperative chemotherapy plus surgery. These findings are significant, because if validated, they suggest that patients with MSI-H or MMRD may not benefit (or may experience a detrimental effect) from perioperative chemotherapy and may be

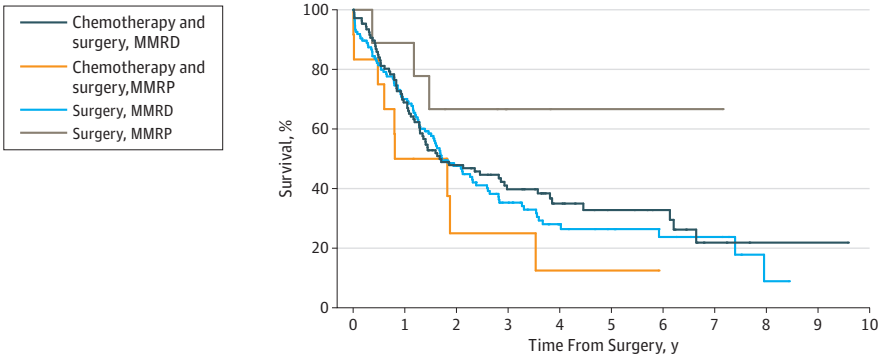
Figure 1. Overall Survival by Microsatellite Instability (MSI) Status and Treatment Arm in the Study Patients



No. at risk										
Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1
Chemotherapy and surgery, MSI-positive patients	9	3	1							
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1	
Surgery, MSI-positive patients	10	8	6	3	1	1				

Patients were dichotomized into 2 groups: high MSI (MSI-H) and microsatellite stable (MSS) or low MSI (MSI-L), which are analyzed separately in each treatment arm. Differences in overall survival were assessed using the Kaplan-Meier method and compared using the log-rank test. The hazard ratios for MSI-H vs MSS or MSI-L were 0.35 (95% CI, 0.11-1.11) for surgery alone (P = .08) and 2.22 (95% CI, 1.02-4.85) for chemotherapy and surgery (P = .04) (interaction P = .01). P < .05 was considered to be statistically significant.

Figure 2. Overall Survival by Mismatch Repair (MMR) Protein Status in the Study Patients



No. at risk										
Chemotherapy and surgery, MMRD	107	73	47	32	19	13	10	3	1	1
Chemotherapy and surgery, MMRP	12	6	2	2	1	1				
Surgery, MMRD	136	92	52	34	18	13	8	6	1	
Surgery, MMRP	9	8	5	2	1	1	1	1		

Patients were dichotomized into 2 groups: MMR deficiency (MMRD) and MMR proficiency (MMRP). The groups are analyzed separately in each treatment arm. Differences in overall survival were assessed using the Kaplan-Meier method and compared using the log-rank test. P < .05 was considered to be statistically significant.

better served by a surgery-only approach. Because MSI or MMRD tumors comprise up to 10% to 20% of stomach cancers in some series, this finding has the potential to affect large numbers of patients.[15]

Our results are consistent with the results of similar previous Asian and Western retrospective studies[8,10,11,13] that found a significant positive prognostic effect of MSI-H status for patients with resected gastric cancer. In our study, MSI-H and MMRD tumors were only detected in patients with gastric cancer; this finding is commensurate with previous studies[15,16] that found a low prevalence of MSI and MMRD in gastroesophageal junction and esophageal tumors. The consistent effect of MSI-H status on prognosis is supported by a pooled analysis[17] of 17 studies that found an HR for OS of 0.76 (95% CI, 0.65-0.88; P < .001) and limited heterogeneity. In contrast, much fewer data are available on the interaction between MSI status and chemotherapy. In this regard, our results are comparable to the 2 largest retrospective Asian studies[9,13] in which patients with resected gastric cancer were treated with postoperative fluoropyrimidine chemotherapy. In these retrospective series, patients with stage II and III MSS cancer derived a benefit from adjuvant fluorouracil-based chemotherapy, whereas patients with MSI-H cancer did not. Although our analysis is post hoc, our study is the first randomized clinical trial, to our knowledge, with a control group to validate these findings.

In colorectal cancer, the putative prognostic effect of MMR protein status on the benefit of adjuvant chemotherapy is limited to patients with stage II disease.[5] This finding is hypothesized to be attributable to the relatively small benefit associated with adjuvant fluoropyrimidine therapy in patients with stage II colorectal cancer and to the postulated effects of MMRD on the DNA damage response to fluoropyrimidines.[18] First, because the relative benefit of perioperative chemotherapy for gastroesophageal cancer is greater than the benefit of adjuvant chemotherapy in stage II colorectal cancer and second, because cisplatin and epirubicin were used in the MAGIC trial in addition to fluorouracil, our results are possibly unexpected (however, because data on complete nodal staging were absent in a substantial percentage of patients, we cannot de-

finitively stage the disease of all patients). One potential explanation for this phenomenon is that the effect of MMRD on the DNA damage response to platinum compounds is differential based on the platinum analog used.[19] The MLH1-deficient cell line models have been reported to be relatively resistant to cisplatin but not oxaliplatin, which in turn reflects the differences in platinum compounds used in the MAGIC trial and colorectal cancer. This circumvention of the DNA damage repair mechanism by oxaliplatin may have important clinical implications; since the MAGIC trial was presented, oxaliplatin has been determined to be clinically equivalent to cisplatin and has replaced it in many gastric cancer chemotherapy regimens.[20] Another hypothesis sidesteps the requirement for chemoresistance: MSI-H tumors are associated with a vigorous immune infiltrate, which may be responsible for suppression of residual micrometastases after surgery.[21,22] Chemotherapy may have a negative effect on this immunosurveillance, thus reducing the innate benefit of the hypermutated phenotype.

Limitations

A potential limitation of our analysis is that the entire MAGIC cohort was not analyzed because we did not receive tissue from all patients. This limitation affects the numbers analyzed in our study. Furthermore, the low prevalence of MSI and MMRD and the number of events limit the statistical reliability of these data, which as a post hoc analysis should be considered exploratory. However, because survival was not significantly different in those who did not have tissue available for analysis, we do not believe there is a significant bias. One potential confounder of our results is that MSI and MMRD tumors were more likely to be of the Lauren intestinal subtype, which may be associated with improved survival outcomes compared with the diffuse subtype.[23,24] However, in multivariate analysis of the MAGIC trial, histologic subtype was not an independent prognostic marker of OS.[25] Because we analyzed only resected specimens that had undergone treatment in the chemotherapy arm of the study, to truly determine the prognostic value of MMRD, evaluation of biopsy specimens is required. However, there is no evidence that MMRD status changes after chemotherapy: the equivalent proportion of patients with MMRD in both arms of the trial support this contention. There is an imperfect correlation between MMRD and MSI assessment in our study. This imperfect correlation may be a result of interobserver variability in immunohistochemical analysis assessment, heterogeneity of biomarker expression in gastric cancer, the presence of normally translated but nonfunctional MMR proteins in the setting of a missense *MLH1* (OMIM 120436) mutation, or other rare genomic defects that result in MSI-H status with intact MMRD function, such as the polymerase DNA ε1 (*POLE*) (OMIM 174762) mutation.[26-28] Although our overall concordance is high, other studies[29,30] in gastric cancer have found lower sensitivities of MMR protein immunohistochemical analysis for detection of MSI-H MMRD. For these reasons, a genomic rather than an immunohistochemical approach may be preferred for patients with gastric cancer. Finally, an alternative hypothesis is that the MSI-H status might be associated with other molecular changes that predispose patients to chemotherapy resistance. In preclinical gastric cancer models, epigenetic changes, such as methylation of bone morphogenetic protein 4 (*BMP4*) (OMIM 112262), are associated with platinum resistance.[31] Clinical data reveal that, in neoadjuvantly treated patients with gastric cancer, those with lower levels of promoter gene methylation have improved survival compared with those with more frequent methylation.[32] Promoter methylation of *MLH1* has also been associated with inferior survival of patients with resected gastric cancer treated with oxaliplatin-based adjuvant chemotherapy.[33] However, because MSI status is not reported in either of these series, the independent contribution of epigenetic changes remains unclear.

Conclusions

We report for the first time, to our knowledge, in a randomized clinical trial of patients with operable gastroesophageal cancer treated with chemotherapy with a surgery-only control group that the presence of MMRD is associated with a positive prognostic effect in patients treated with surgery alone and a differentially negative prognostic effect in patients treated with chemotherapy plus surgery. If validated, this finding has the potential to improve patient selection for perioperative chemotherapy and spare a significant proportion of patients with gastric cancer unnecessary treatment. We do not believe that these data justify a change in clinical practice; however, we recommend prospective trial validation to ascertain the optimal perioperative treatment for patients with MSI-H gastric cancer. In light of the remarkable success of anti–programmed cell death protein 1 therapies in MMRD colorectal cancer, alternative treatment strategies could be reasonably investigated for these patients.[24]

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